Amendments to the Drawings

The attached sheet of drawings includes changes to FIG. 4D. This sheet, which includes FIGS. 4C and 4D, replaces the original sheet including FIG. 4C and 4D. In FIG. 4D, a line running across the figure, which was erroneously included in the original sheet, is removed.

Attachment: Replacement Sheet
Annotated Sheet Showing Changes

REMARKS

Claims 1-59, as amended, and new claim 60 appear in this application for the Examiner's review and consideration. Claims 1, 2, 3, 6, 13, 34, 36, 39, 41 and 54 are amended for clarity and to further define the preferred embodiments of the invention. New claim 60 is directed to a preferred formulation that recites the relative amounts and most desirable components. In addition, FIG. 4D of the drawings is amended to remove a line that was erroneously included in the figure. Support for the amendments appear in the specification as well as the original claims. As no new matter is introduced by any of these changes or additions, their entry is warranted at this time.

Claims 1-28, 30-47, and 56-59 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-26 of co-pending Application No. 10/798,161 in view of U.S. Patent No. 5,922,349 to Ellisen et al. As the copending application has not been yet allowed, the provision has not occurred and this rejection should be withdrawn so that the present application can be allowed. With the removal of this rejection, claims 37-47 and 56-59 should be allowed since no other rejections were made as to those claims.

Claims 13-36 and 48-55 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement for the reasons stated on pages 2-4 of the Office Action. Applicants respectfully traverse.

It is well known to a person having ordinary skill in the art to use hormonal or non-hormonal active agents to treat hormonal disorders. Among others, examples of treatment of hormonal disorders using non-hormonal active agents are provided in PHARMACOTHERAPY - A PATHOPHYSIOLOGICAL APPROACH, 5th ed., J. T. Dipiro et al., Sections 8-9, pp. 1335-1510 (McGrow-Hill Medical Publishing Division, 2002).

As this reference provides, a hormone is a substance produced by a gland or a tissue and transported by the blood to act on a distant organ or tissue. Examples of hormones include insulin, somatotropin (growth hormone), follitropin, estradiol, testosterone, progesterone, thyroxine, and triiodothyronine. While a hormonal disorder may be treated by supplying a

deficient hormone, use of non-hormone drugs for treating hormonal disorders is also well known.

For example, diabetes, which is caused by absolute or relative deficiency of insulin, can be treated, depending on the severity of the deficiency, with hormone replacement (e.g., administration of insulin) or with non-hormone drugs such as sulfonylureas (e.g., acetohexamide, chlorpropamide, tolazamide, tolbutamide, glimepiride, glipizide, glyburide), short-acting insulin secretagogues (e.g., nateglinide, repaglinide), biguanides (e.g., metformin), glitazones (e.g., pioglitazone, rosiglitazone), and alpha-glucosidase inhibitors (e.g., acrabose, miglitol). Thyroid disorders can also be treated with hormone replacement therapy or with non-hormonal active agents, such as propylthiouracil, methimazole, propanolol, and nadolol. Adrenal gland disorders, such as Cushing's syndrome, can be treated with non-hormonal active agents such as metapyrone, aminoglytethimide, cyproheptadine, mitotane, and ketoconazole. Growth hormone excess can be treated with non-hormonal active agents such as dopamine agonists (e.g., bromocriptine, pergolide, lisuride, and cabergoline), octreotide, and lantreotide. Hyperprolactinemia can also be treated with dopamine agonists. Hormone-caused infertility can be treated with non-hormonal active agents such as clomiphene, nafarelin, leuprolide, ganirelix, and cetrorelix. Estrogen deficiency can be treated with non-hormonal selective estrogen-receptor modulators such as tamoxifen and raloxifene. These illustrative and non-limiting examples of non-hormonal active agents are well known to a person skilled in the art and are widely used to treat hormonal disorders.

Because, as the above examples show, the use of certain hormonal or non-hormonal active agents to treat a given hormonal disorder is well known in the art, practicing the invention according to claims 13-36 and 48-55 would not require undue experimentation. In addition, for clarity, claims 13 and 34 were amended to state that the active agent is one that is effective for treating at least one symptom of the hormonal disorder to be treated. A skilled artisan has the requisite knowledge of such active agents. Furthermore, claims 15-31 and 34-36 recite specific active agent(s), so that these claims should not have been subject to this rejection. As explained in the specification, rather than identifying new active agents, the invention is directed to a formulation for transmucosal or transdermal delivery of active agents by the use of a new delivery system comprising a unique combination of solvents and permeation enhancers that is not known, disclosed or taught by the prior art. Accordingly, Applicants respectfully request that

the rejection under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement be withdrawn. With the removal of this rejection, claims 13-33 and 48-55 should also be allowed since no prior art rejections apply to those claims.

Claims 1-12 and 34-36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons set forth on page 5 of the Office Action. In response, claims 1 and 34 are amended to clarify that when the active agent is estrogen, progestin is not present in the formulation in a therapeutically effective amount, and when the active agent is progestin, estrogen is not present in the formulation in a therapeutically effective amount. Accordingly, this rejection has been overcome and should be withdrawn. Thus, claims 4-6 and 34-36 are now allowable since these claims also were not rejected over the prior art.

Claims 1-3 and 7-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,891,462 to Carrara ("the '462 patent"). The Examiner specifically relies upon Examples 5-7 and Examples 8-9 and 1 in Table III of the '462 patent.

This patent is owned by applicants' assignee, so that it is not an unfamiliar document. In fact, the teachings and disclosure of this patent were carefully analyzed when formulating the present claims. This is one reason for the proviso in claim 1 that when the active agent is estrogen, progestin is not present in the formulation in a therapeutically effective amount, and when the active agent is or progestin, estrogen is not present in the formulation in a therapeutically effective amount. Claim 1 also excludes detectible amounts of long-chain fatty alcohols, long-chain fatty acids and long-chain fatty esters to avoid undesirable odor and irritation from such compounds during use of the formulation, whereas the '462 patent teaches the benefits of using such components, as exemplified by the use of lauryl alcohol.

Also, the examples noted by the Examiner are directed to formulations which either do not contain a permeation enhancer of diethylene glycol mono ethyl ether (TC) (Examples 5-7) or contain both TC and lauryl alcohol (LA) (Examples 8-9, 1). The '462 patent does not provide a comparison of a formulation that does not contain TC with a formulation which contains TC as the only permeation enhancer. This is significant because, as is known in the art, the concentration of a permeation enhancer can directly influence permeation of the active agent. For example, providing too much of a permeation enhancer can actually impair permeation of the active agent. In Examples 1 and 8-9 of the '462 patent, the concentration of 2% lauryl alcohol may be too great such that it has a negative effect on estradiol permeation, counter-

balancing the positive effect of TC. Such negative effect of 2% lauryl alcohol would explain why there is no significant difference in estradiol permeation rate between Examples 5 and 8 and between Examples 7 and 1 of the '462 patent.

To further illustrate this point, Applicants have performed an *in vitro* permeation study comparing the effects of TC 5% in combination with LA 2% ("Formulation EG064") versus TC 5% alone ("Formulation Eg063") on skin permeation of estradiol. The composition of each formulation is presented in Table 1.

Table 1. Compositions for Examples A and B in *in vitro* permeation study (as expressed in % wt)

	Formulation Eg064	Formulation Eg063
17-βEstradiol	0.06	0.06
Ethanol	48.5	48.5
Propylene glycol	6.00	6.00
Diethylene glycol mono ethyl ether	5.00	5.00
Lauryl alcohol	2.00	-
EDTA disodium	0.06	0.06
Carbomer C980 NF	1.20	1.20
Triethanolamine	0.35	0.35
Purified water	QS 100.0	QS 100.0

The results of the study show that Formulation Eg063 delivers about 80% more estradiol through the skin than Formulation Eg064 after 24 hours, resulting in the cumulated drug permeation of about 1.172 $\mu g/cm^2$, compared to 0.662 $\mu g/cm^2$ of Formulation Eg064. The results are graphically illustrated below. This study demonstrates the advantages of a formulation which includes the novel delivery system according to the present claims and which is substantially free of long-chain fatty alcohols, long-chain fatty acids and long-chain fatty esters, over a formulation containing both TC and LA according to Examples 8, 9, and 1 of the '462 patent, and a formulation containing neither TC nor LA according to Examples 5-7 of the '462 patent.

Annotated Sheet Showing Changes

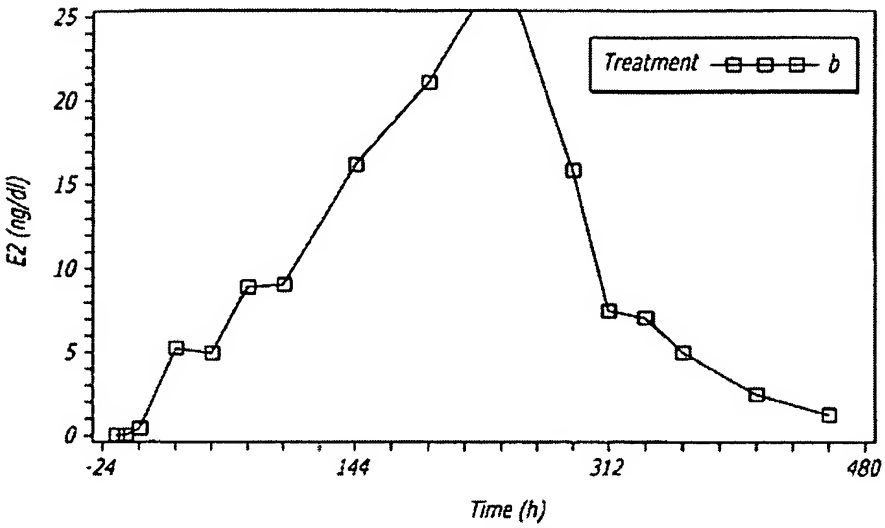


FIG. 4C

Deleted

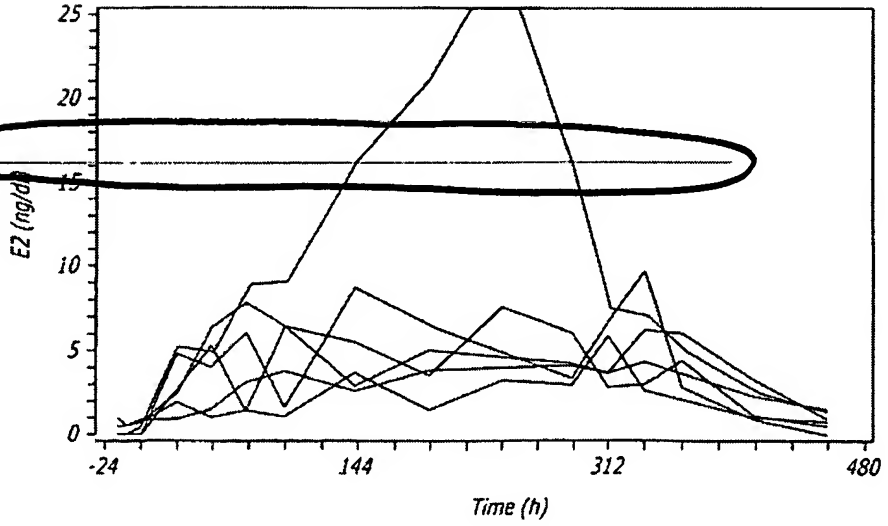
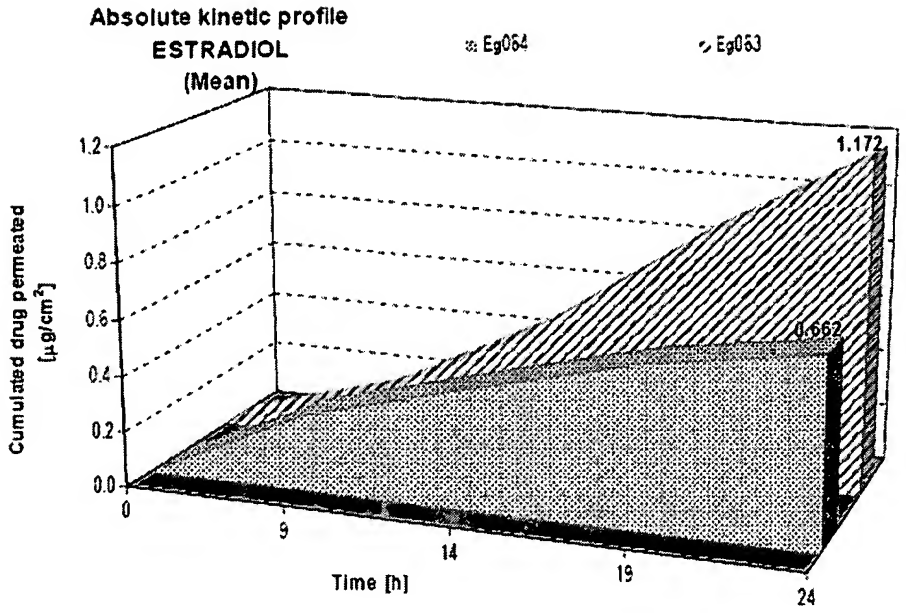


FIG. 4D



Furthermore, dependent claims 2-3 and 7 recite preferred delivery systems that provide optimum transmucosal or transdermal formulations. These claims (as well as claims 4-6 that were not rejected over the patent) are allowable due to their further distinctions from the '462 patent. Thus, the rejection based on that patent has been overcome and should be withdrawn

In view of the above, it is believed that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree, then a telephonic or personal interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the claims.

Respectfully submitted,

4/20/06
Date

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